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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANGELO GUGLIELMOTTI, LORENZO POLENZANI,
ALESSANDRA ALISI and NICOLA CAZZOLLA

Appeal[1] 2009-007941
Application 10/560,836
Technology Center 1600

Decided: May 14, 2010

Before ERIC GRIMES, JEFFREY N. FREDMAN, and STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method for treating neuropathic pain. The Patent Examiner rejected the claims on the ground of obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

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[1] Oral hearing held April 22, 2010.

STATEMENT OF THE CASE

The Specification cites European patent application EP-A-0 630 376 for its disclosure of "a large number of compounds of formula I," said to be "active in the treatment or the prophylaxis of gastrointestinal, cardiac and central nervous system disorders." (Spec. 1:6-14.) The Specification discloses that compounds of formula I in which substituent "R" is H, a linear or branched alkyl chain having from 1 to 12 carbon atoms or an arylalkyl radical, are "particularly active in neuropathic pain."[2] (*Id.* at 1:10-18.) The Specification designates that subgenus of formula I as "Compound (I)." (*Id.*) "Typical examples of pathological conditions characterized by neuropathic pain are diabetes, cancer, immunodeficiency, traumas, ischaemia, multiple sclerosis, sciatic neuralgia, trigeminal neuralgias and post-herpetic syndromes." (*Id.* at 2:29-3:2.) The Specification states that "[t]he analgesic activity of Compound (I) has been proved by means of two experimental models in the rat: allodynia[3] induced by ligature of the sciatic nerve and mechanical hyperalgesia in diabetic neuropathy induced by streptozotocin." (*Id.* at 4:14-17.)

Claims 6-12 and 14-23, which are all the pending claims, are on appeal. Claims 6, 18 and 20 are representative and read as follows:

6. A method for the treatment of neuropathic pain comprising: administering to a subject in need thereof a compound of formula I:

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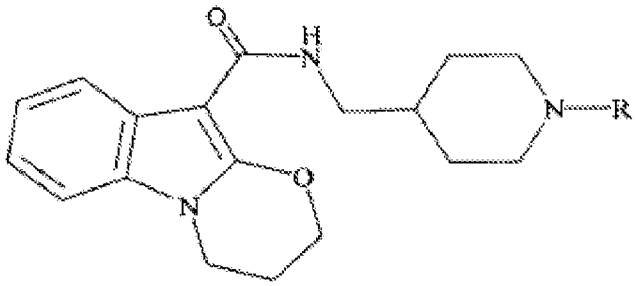
[2] According to an article Appellants provide from MedicineNet.com, "[n]europathic pain is a complex, chronic pain state that usually is accompanied by tissue injury." (App. Br., Evid. Appx.)

[3] According to an article Appellants provide from Wikipedia, "[a]llodynia, meaning 'other pain', is an exaggerated response to otherwise non-noxious stimuli and can be either static or mechanical." (App. Br., Evid. Appx.)



wherein
R is H, a linear or branched alkyl chain having from 1 to 12 carbon atoms, or an arylalkyl group;
or a pharmaceutically acceptable acid-addition salt thereof.

18. The method of claim 6, wherein said subject has neuropathic pain associated with diabetes.

20. The method of claim 6, wherein said subject has neuropathic pain associated with immunodeficiency, trauma, ischaemia, multiple sclerosis, sciatic neuralgia, trigeminal neuralgia or a post-herpetic syndrome.

The Examiner rejected the claims as follows:

- claims 6-12 and 14-17 under 35 U.S.C. § 103(a) as unpatentable over Gaster,[4] Smith[5] and Jørum;[6]

- claims 6-12 and 14-17 under 35 U.S.C. § 103(a) as unpatentable over Gaster, Burstein[7] and Jørum;

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[4] EP 0630376 B1, issued to Laramie Mary Gaster et al., June 2, 1999.
[5] M.I. Smith et al., *5-HT_4 receptor antagonism potentiates inhibition of intestinal allodynia by 5-HT_3 receptor antagonism in conscious rats*, 271 NEUROSCIENCE LETTERS 61-64 (1999).
[6] E. Jørum et al., *Cold allodynia and hyperalgesia in neuropathic pain: the effect of N-methyl-D-aspartate (NMDA) receptor antagonist ketamine—a double blind, cross-over comparison with alfentanil and placebo*, 101 PAIN 229-235 (2003).

• claims 18-20 under 35 U.S.C. § 103(a) as unpatentable over Gaster, Smith, Jørum and Wickenden;[8] and

• claims 20-23 under 35 U.S.C. § 103(a) as unpatentable over Gaster, Smith, Jørum and Omoigui.[9]

Claims 7-12 and 14-17 have not been argued separately and therefore stand or fall with claim 6. Claims 19 and 20 have not been argued separately with respect to the third rejection and therefore stand or fall with claim 18 for that rejection. Claims 21-23 have not been argued separately with respect to the fourth rejection and therefore stand or fall with claim 20 for that rejection. 37 C.F.R. § 41.37(c)(1)(vii).

OBVIOUSNESS

The Issue

The Examiner's position is that Gaster taught the compounds of formula 1 as 5-HT4 receptor antagonists and taught administering the compounds to treat conditions including migraine, but did not teach treating neuropathic pain. (Fin. Rej. 3-4.) The Examiner found that Smith taught that 5-HT4 receptor antagonists inhibit intestinal allodynia, and that Jørum taught that allodynia and hyperalgesia were frequent clinical findings in patients with neuropathic pain. (*Id.* at 4.) The Examiner reasoned that inhibiting allodynia as Smith taught would provide a method of treating

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[7] Rami Burstein et al., *The development of cutaneous allodynia during a migraine attack*, 123 BRAIN 1703-1709 (2000).
[8] Alan David Wickenden et al., *Methods For Treating Or Preventing Pain*, US 6,326,385 B1 (Dec. 4, 2001).
[9] Osemwota Omoigui, *Method Of Treatment Of Persistent Pain*, US 2004/0038874 A1 (Feb. 26, 2004).

neuropathic pain because Jørum taught that allodynia was a frequent finding in patients with neuropathic pain. (*Id.*) The Examiner concluded it would have been obvious to use one of Gaster's 5-HT4 receptor antagonists in place of Smith's 5-HT4 antagonist in the treatment of neuropathic pain. (*Id.*)

The Examiner found that Burstein taught "that most migraine patients exhibit cutaneous allodynia during a fully developed migraine attack," but Burstein did not identify allodynia as neuropathic pain. (*Id.* at 5.) The Examiner concluded it would have been obvious to use the compounds of formula I in the treatment of neuropathic pain because (i) Gaster taught their administration in relieving migraine attack, (ii) Burstein taught that allodynia was exhibited during a migraine attack, (iii) Jørum taught that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain, and (iv) "by treating migraine attacks in patients allodynia is treated and in turn the neuropathic pain." (*Id.*)

Addresing claims 18-20, the Examiner found that while Gaster, Smith and Jørum did not disclose that neuropathic pain was associated with diabetes, cancer, or trigeminal neuralgia, Wickenden taught that neuropathic pain was associated with injury to the central or peripheral nervous system due to cancer, diabetes, diabetic neuropathy, or trigeminal neuralgia. (*Id.* at 5-6.) Reasoning again that Gaster, Smith and Jørum suggested treating neuropathic pain with Gaster's compounds, the Examiner concluded that it would have been obvious to use the same compounds to treat neuropathic pain associated with the neuropathic conditions discussed by Wickenden.

Addressing claims 20-23, the Examiner found that Omoigui taught a method of treating persistent pain disorders including neuropathic pain by

administering a serotonin receptor antagonist. (*Id.* at 7.) According to the Examiner, Omoigui disclosed that (i) inflammation was the underlying basis for pain, including neuropathic pain, (ii) antagonizing the inflammatory response will relieve pain of every type, (iii) chronic allodynia and hyperalgesia are hallmarks of neuropathic pain, and (iv) persistent pain disorder is neuropathic pain, including neuralgia and post herpetic neuralgia. (*Id.*) In view of Omoigui's teaching to administer serotonin receptor antagonists, the Examiner concluded it would have been obvious to administer Gaster's serotonin receptor antagonist compounds to treat neuropathic pain such as trigeminal neuralgia or post herpetic syndrome. (*Id.*)

Appellants dispute that the prior art provided a reasonable expectation of success that a compound of formula I could have been used to treat neuropathic pain. (App. Br. 12.) Appellants contend that "[n]europathic pain is a specific type of pain associated with nerve damage that is distinct from nociceptive pain (pain sensed by undamaged nervous tissue)." (*Id.* at 13.) Appellants argue that Gaster "does not disclose or suggest use of [its] compounds for treating neuropathic pain associated with damaged nerves." (*Id.* at 14.) "The Examiner is alleging that 5-HT receptor antagonists generally ameliorate neuropathic pain, but there is no support in the prior art for this allegation." (*Id.*) "Moreover, the thermal allodynia (Jørum) and mechanical allodynia (Smith) are distinct from one another and involve different types of nociception." (*Id.*) Further, Appellants read Smith to teach only that "5-HT4 receptor antagonism potentiates inhibition of intestinal allodynia by 5-HT3 receptor antagonism" and as "not disclos[ing] that a 5-HT4 receptor antagonist would have any effect on

intestinal allodynia in the absence of a 5-HT3 receptor antagonist." (*Id.* at 15.)

Concerning the Omoigui publication, Appellants argue that the content of papers on which the publication is based "is highly speculative and theoretical, . . . and provides no reasonable expectation of success for treating neuropathic pain using a compound of formula I." (*Id.* at 21.)

Appellants further contend that the Examiner used a hindsight approach. (Reply Br. at 2.) "The missing link in the Examiner's argument [is] any nexus in the prior art that the pain disorders described by Gaster and Smith are mediated by the same mechanism as those responsible for causing neuropathic pain, and that the mechanism causing neuropathic pain is targeted by the compound of formula (I)." (*Id.*) According to Appellants, "[b]oth allodynia and hyperalgesia are generic clinical findings of different pathologic states having different origins . . . . The prior art does not provide a reasonable expectation that pain, including allodynia or hyperalgesia, associated with radically different disorders having different etiologies and pathological manifestations, could be treated with the same compound." (*Id.* at 3.)

Findings of Fact

1. Gaster taught that compounds of formula (I) have 5-HT_4 receptor antagonist activity. (Gaster, 2:[0006] and [0007].)
2. The Examiner found that Gaster taught a method of treating irritable bowel syndrome, migraine, and other conditions, by administering a compound of formula (I). (Ans. 3, citing Gaster 6:42-43.)

3. The Examiner found that Gaster did not teach a method of treating neuropathic pain. (*Id.*)
4. The Examiner found that Smith taught that a 5-HT4 receptor antagonist such as SB 207266 potentiated inhibition of intestinal allodynia. (*Id.* at 4, citing Smith at Abstract and at 63:11-12.)
5. Smith disclosed that their data "suggests that 5-HT_4 receptor activation enhances the ability of 5-HT_3 receptor activation to induce intestinal allodynia." (Smith, Abstract.)
6. The Examiner found Jørum taught that "allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain." (Ans. 4, citing Jørum 229:1-5.)
7. The Examiner found that "inhibiting allodynia in patients provides a method of treatment of neuropathic pain." (Ans. 4.)
8. The Examiner found that one of ordinary skill in the art would have been motivated to use one of Gaster's compounds in place of Smith's compound to treat allodynia. (Ans. 4.)
9. Burstein disclosed that "most migraine patients exhibit cutaneous allodynia inside and outside their pain-referred areas when examined during a fully developed migraine attack." (Burstein, Abstract.)
10. Wickenden disclosed that neuropathic pain can be caused by injury to the central or peripheral nervous system due to cancer, diabetes, diabetic neuropathy, or trigeminal neuralgia. (Wickenden, col. 27, claim 8.)
11. Omoigui's disclosure related to a method for treating persistent pain by inhibiting mediators of inflammation including serotonin. (Omoigui, Abstract.)

12. Omoigui taught: "antagonism of inflammation and the inflammatory response will relieve pain of every origin, type and character." (*Id.* at 1:[0004].)

13. Omoigui taught: "[t]he hallmarks of neuropathic pain are chronic allodynia and hyperalgesia." (*Id.* at 8:[0072].)

14. Embodiments of Omoigui's method included treating "neuropathic pain syndrome including neuralgia or nerve pain, . . . post herpetic neuralgia" (*id.* at 11, claim 12), and administering a serotonin receptor antagonist (*id.* at 13, claim 80).

15. According to an article entitled "Migraine" in the Evidence Appendix provided with the Appeal Brief:

> [m]igraine was once thought to be initiated by problems with blood vessels . . . Current thinking is that a phenomenon known as cortical spreading depression is responsible for the disorder. In cortical spreading disorder, neurological activity is depressed over an area of the cortex of the brain. This situation results in the release of inflammatory mediators leading to irritation of cranial nerve roots, most particularly the trigeminal nerve, which conveys the sensory information for the face and much of the head.
>
> (Migraine, pagina 3 di 8.)

15. The Specification states: "[t]he analgesic activity of Compound (I) has been proved by means of two experimental models in the rat: allodynia induced by ligature of the sciatic nerve and mechanical hyperalgesia in diabetic neuropathy induced by streptozotocin." (Spec. 4:14-17.)

16. According to the Specification, the model based on ligature of the sciatic nerve "is well known … [as] an effective instrument for the

study of drugs for use in the treatment of neuropathic pain in man and, in particular, in the control of conditions such as allodynia and hyperalgesia." (*Id.* at 4:21-5:2.)

Principles of Law

"Obviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

Analysis

A. The rejections of claims 6-12 and 14-17 over Gaster, Smith, Jørum and claims 18-20 over Gaster, Smith, Jørum and Wickenden.

According to the rejections, a key finding links the teachings of these references: that Smith taught that the 5-HT4 receptor antagonist SB 207266 showed an anti-allodynic activity. (Ans. 4.) Appellants dispute that the evidence supports that finding. (App. Br. 15.) Appellants argue that Smith "does not disclose that a 5-HT4 receptor antagonist would have any effect on intestinal allodynia in the absence of a 5-HT3 receptor antagonist." (*Id.*, emphasis deleted.) Instead, according to Appellants, Smith "only indicates that 5-HT4 receptor antagonists potentiate inhibition of intestinal allodynia by a 5-HT3 receptor antagonist." (*Id.*, emphasis deleted.)

We agree that Smith did not disclose administering a 5-HT4 receptor antagonist without a 5-HT3 receptor antagonist, and that Smith described the role of the 5-HT4 receptor antagonist as potentiating the 5-HT3 receptor antagonist. That evidence does not support finding that Smith described an anti-allodynic effect attributable to a 5-HT4 receptor antagonist alone, and

we find the other references do not make up for that deficiency. Without more, the evidence is insufficient to support finding an expectation of success in these references.

B. The rejection of claims 6-12 and 14-17 over Gaster, Burstein and Jørum.

Burstein disclosed that most migraine patients exhibit cutaneous allodynia. (FF 9.) Gaster taught treating migraine with a serotonin receptor antagonist (FF 2), but did not teach treating neuropathic pain (FF 3). The rejection reasons that one of skill in the art would have used Gaster's compounds to treat migraine, and in so doing would have treated allodynia. The rejection concludes from this that "[h]ence by treating migraine attacks in patients allodynia is treated and in turn the neuropathic pain." (Ans. 5.) The missing link is evidence that allodynia means neuropathic pain is present. On this record, there is no evidence that allodynia means that neuropathic pain is necessarily present or that migraine is neuropathic. Jørum taught that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain (FF 6), but Jørum does not supply the missing evidence.

C. The rejection of claims 18-20 over Gaster, Smith, Jørum and Omoigui.

We earlier found that Smith did not support finding an expectation of success for treating neuropathic pain. In contrast to the earlier rejection, Smith is here combined with Gaster, Jørum and Omoigui. Omoigui explicitly taught treating neuropathic pain with a serotonin receptor

antagonist. (FF14.) Given Omoigui's direct teaching, we agree with the Examiner that it would have been obvious to use one of Gaster's serotonin receptor antagonists to treat neuropathic pain.

Appellants argue that little weight should be given to Omoigui's association of neuropathic pain with inflammation because "these teachings are merely hypothetical and theoretical." (App. Br. 20.) Osemwota Omoigui's patent application publication references "Sota Omoigui's Law" concerning pain. (*See* Omoigui, 1:[0001].) In the "Evidence Appendix" to their brief, Appellants provide copies of two articles published by Sota Omoigui in the journal *Medical Hypotheses*, and the "Guide for Authors" from the journal. According to Appellants, "the content of these literature references . . . provides no reasonable expectation of success for treating neuropathic pain using a compound of formula I." (App. Br. 21.) "Moreover, a plain reading of Omoigui [0051] and [0068-0069] does not reveal a common mechanism linked to Substance P between the naturopathic pain and pain associated with migraine." (*Id.*)

We find Appellants' evidence and argument insufficient to discount Omoigui's published patent application. First, the rejection relied on the published patent application as evidence concerning the state of the prior art; it did not rely on the articles Appellants provide. We find that the arguments about the *Medical Hypotheses* journal are beside the point. Further, while the journal's "Guide for Authors" indicates that the journal "will consider" speculative ideas, that does not mean that a person of ordinary skill in the art would have rejected published hypotheses as per se unreliable. We also find Appellants' discussion of Substance P misdirected. The Examiner relied on

Omoigui's instruction to use a serotonin receptor antagonist, and not the portion of Omoigui that discussed Substance P.

CONCLUSIONS

A. Gaster, Smith and Jørum, taken as a group with or without Wickenden, did not provide sufficient evidence to support finding an expectation of success for administering a Gaster compound to treat neuropathic pain.

B. Gaster, Burstein and Jørum, taken as a group, did not provide sufficient evidence to support finding an expectation of success for administering a Gaster compound to treat neuropathic pain.

C. Gaster, Smith, Jørum and Omoigui, taken as a group, provided sufficient evidence to support finding an expectation of success for administering a Gaster compound to treat neuropathic pain.

SUMMARY

We reverse the rejection of claims 6-12 and 14-17 under 35 U.S.C. § 103(a) as unpatentable over Gaster, Smith and Jørum; and we reverse the rejection of claims 18-20 under 35 U.S.C. § 103(a) as unpatentable over Gaster, Smith, Jørum and Wickenden.

We reverse the rejection of claims 6-12 and 14-17 under 35 U.S.C. § 103(a) as unpatentable over Gaster, Burstein and Jørum.

We affirm the rejection of claims 20-23 under 35 U.S.C. § 103(a) as unpatentable over Gaster, Smith, Jørum and Omoigui.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

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